Descriptive Study of a 488 Patients Cohort with Inherited Retinal Diseases and a Low Genetic Diagnosis Rate.

Rosa M. Coco-Martin (✉ rosa@ioba.med.uva.es)

Instituto de Oftalmobiología Aplicada: Instituto de Oftalmobiología Aplicada

Miguel Diego-Alonso

Instituto de Oftalmobiología Aplicada

W. Andres Orduz-Montaña

Instituto de Oftalmobiología Aplicada: Instituto de Oftalmobiología Aplicada

M. Rosa Sanabria

Complejo Asistencial de Palencia

Hortensia Sanchez-Tocino

Hospital Universitario Rio Hortega de Valladolid: Hospital Universitario Rio Hortega

Research article

Keywords: inherited retinal dystrophies, retinitis pigmentosa, genetic diagnosis, visual acuity, visual field

Posted Date: September 22nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-78231/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: To analyze the distribution of inherited retinal diseases (IRDs), describe the clinical characteristics of patients, and determine the percentages of patients with genetic diagnoses in the Castilla and Leon region of Spain.

Methods: All patients with an IRD seen in the two major referral units of Castilla y Leon during a 20-year period were included. The ages at symptom onset, diagnosis, and the last visit; sex; family history; history of consanguinity; type of inheritance; status of the fundus and electroretinogram; lens and macular status, visual acuity; and visual field data were recorded. Patients were divided into those with retinitis pigmentosa (RP) and all others. The genetic mutations were gathered.

Results: Four hundred eighty-eight patients with IRDs were studied, 216 with RP (of which 15.74% had syndromic disease) and 272 with other conditions (59.19% of which were macular dystrophies). A genetic study had been performed in 27.31% of patients (29.31% of which were negative) among the patients with RP and in 26.1% of the rest of the IRDs (28.16% of which were negative). In the group without a genetic diagnosis, 70.6% of subjects had good remaining vision. The mean delay in diagnosis was 6-16.2 years.

Conclusions: The percentage of patients with IRDs that are candidates for undergoing personalized treatments including gene therapy in our region is low and must be improved. Most patients with RP who did not undergo a genetic study have good remaining vision, so they would be candidates for receiving treatments aimed at maintaining vision. There is a significant delay in diagnosis.

Background

Inherited retinal diseases (IRD) are a group of rare Mendelian neurodegenerative conditions caused by mutations in genes that code for proteins essential for the functioning and maintenance of photoreceptors, retinal pigment epithelium and other retinal neurons leading to retinal dystrophies or optic neuropathies [1]. The prevalence rates vary between 1/750 and 1/5,000, depending on the region and level of consanguinity or ethnicity [2–4]. IRDs also are one of the main causes of irreversible blindness in young patients and have a highly significant impact on quality of life and health economics [5, 6].

IRD can be classified as panretinal pigmentary retinopathies affecting primarily rods or cones in which pigmentary clumping occurs secondary to photoreceptor death; macular dystrophies with only central retinal involvement; stationary conditions in which the photoreceptors do not function but do not die; optic nerve disease primarily due to involvement of ganglion cells; and other less frequent diseases such as vitreoretinopathies [7, 8]. The most frequent IDR is retinitis pigmentosa (RP) that usually is an isolated ocular condition, but 20–30% of cases may be syndromic [2, 9, 10].

The inheritance patterns of these pathologies are usually monogenic, autosomal dominant (AD), autosomal recessive (AR), or X-linked recessive (XL) but on rare occasions can be digenic, mitochondrial,

or have another pattern [2]. More than 3,000 mutations have been identified in more than 300 genes in syndromic and non-syndromic diseases, and that number is constantly increasing thanks to greater access to next-generation sequencing (NGS) [5, 11].

Creation of organized and shared networks to create registries and biobanks would facilitate the performance of epidemiologic studies and identify the causal mutations using exome and whole genome sequencing provided by the NGS techniques, which has become an endeavor of the highest priority [5]. This advancement is crucial to elucidate the molecular pathologies of disease, diagnose unresolved cases, improve genetic counseling, and develop new advanced therapies including gene therapy, all of which will change the paradigm of IRDs, as new treatments may improve vision and prevent blindness [12]. Thus, identifying the genes involved and the clinical status of our patients will help identify patients who are candidates for treatments based on personalized medicine or involvement in one of the more than 300 ongoing clinical trials for this group of diseases [13].

The objective of the current study was to describe the relative frequencies of different diseases with the clinical patterns of various subtypes of monogenic retinal degenerations and estimate the molecular diagnostic success rates in describing the causative genes in a Spanish region. This study will increase the knowledge about these dystrophies in our population and provide information to investigators and the public health system.

Methods

This retrospective, cross-sectional, descriptive study was performed at the Instituto Universitario de Oftalmobiología Aplicada (IOBA) Retina Unit, University of Valladolid, Spain, and the RP Unit of the Río Hortega University Hospital (RHUH), Valladolid, Spain, both referral centers in the Castilla y León area, a sparsely populated region with only 2,500,000 inhabitants.

This study followed the tenets of the Helsinki Declaration of 1964 (last amendment, 2013). The Clinical Research Ethics Committee of the Valladolid East Health Area approved the study with appropriate participants' informed consent.

Patients

The RHUH database included 82 patients with RP seen between 1995 and 2019. The IOBA database included 518 consecutive patients with a diagnosis of an IRD seen between 1998 and 2019. All double entries in both units and cases with a doubtful diagnosis (those cases without clear clinical findings or genetically confirmed diagnosis) or an incomplete dataset were excluded.

Data collection

For the RP group, the variables studied included sex; ages at symptom onset, diagnosis, and the last visit; family history; lens status; inheritance pattern, and genetic testing data. The electrophysiology status was recorded as normal, diminished, or abolished for the scotopic and photopic responses. The ocular fundus

was classified as having a classic pattern in the spicules, scarce pigment, granular pattern, atrophy, perivenous pattern, and sector RP. The macular status was classified as preserved, atrophic, or edematous based on ocular fundus, autofluorescence and Spectral Domain Optical Coherence Tomography. The best-corrected visual acuity (BCVA) was recorded using a Snellen chart and converted to the logarithm of the minimum angle of resolution (logMAR) using a validated procedure [14]. The BCVA was collected for each decade of life for each eye; for analysis, the patients were divided into five groups according to the low vision scale of the World Health Organization based on the BCVA in the eye with the better vision, i.e., no low vision (LV) (logMAR < 0.20), mild LV (logMAR > 0.20–0.50), moderate LV (> 0.50 and < 1.00), severe LV (1.00–1.30), and blindness (> 1.30). The visual field (VF) data were divided into five groups: central VF < 5°; central VF between 5° and 10°; central VF > 10°; total abolition of the VF; and central rather than peripheral involvement.

For the remaining IRD patients, we recorded the age; sex; baseline BCVA; ages at symptom onset and diagnosis; inheritance pattern, and mutated gene if available.

Statistical analysis

For the quantitative variables, the descriptive statistics used were the mean, standard deviation (SD), and the range (maximal and minimal values). These values were calculated in Excel tables and with the SPSS program version 24 for Windows (IBM Corp., Armonk, NY, USA) for 1989–2017. For the qualitative variables, the numbers and percentages of each category were used.

The Student's t-test was used to compare the means between two groups for quantitative variables, and the χ^2 test for qualitative variables through a contingency table or Fisher's exact test if the expected frequencies were small. $P < 0.05$ was considered significant. The analyses were performed with the statistical package SPSS, version 24.

Results

The clinical records of 600 patients were reviewed with suspected IRD, and the hereditary cause could only be clinically confirmed in 488 patients. Ultimately, 216 (44.26%) patients with RP and 272 (55.74%) patients with different IRDs were included. Of the later, 39 (7.99%) patients had other panretinal pigmentary retinopathies, 161 (32.99%) had macular dystrophies, 28 (5.7%) stationary diseases, 14 (2.87%) inherited vitreoretinopathies, and 12 (2.46%) optic nerve diseases.

Of the RP subgroup, 112 (51.85%) were men and 104 (48.15%) were women. Thirty patients (13.9%) had Usher syndrome (7 type I, 21 type II, and 2 type III). Two patients had Bardet-Biedl syndrome, one retinal degeneration related to Sjögren-Larsson syndrome and one to Crouzon syndrome. The inheritance pattern could not be established in 28 patients due to lack of information. Of the remaining 194 patients, 47 (24.23%) were classified as sporadic cases, 104 (53.61%) with AR, 29 (14.95%) as AD, 13 (6.7%) as XL, and one (0.52%) with dominant XL that may also be a severe female carrier. In the syndromic RP group, 19 patients (66.33%) were AR and eight (26.66%) were sporadic. The family history was positive in 105

(48.61%) patients of the total RP sample. Twenty-one (11.11%) of 189 patients were children of consanguineous parents and 33 (17.46%) of “relative” consanguineous parents (both born in a village with less than 500 inhabitants).

The mean age of symptom onset in patients with RP was 17.30 ± 15.27 years (range, 1–73) and the mean age at diagnosis was 31.48 ± 17.68 years (range, 2–82) years, indicating an average delay in diagnosis of 16.21 years. No significant differences were found between the mean ages of syndromic RP and non-syndromic RP or between the different patterns of inheritance.

Electroretinography (ERG) data were collected from 69 individuals with RP. The scotopic ERGs was not available in 2 patients (2.94%), it was decreased in 15 (21.74%), and abolished in 51 (73.91%). The photopic ERGs were normal in six (8.69%) patients, 18 (26.09%) had a diminished recording, and 45 (65.22%) had an abolished registry.

The ocular fundus could be classified in 211 patients with RP; of those, 166 (78.67%) had a classical pattern of the spicules, 28 (13.27%) had no a pigment fundus, eight (3.79%) had extensive atrophy, six (2.84%) had sector RP, two (2.84%) perivenous RP, and one (1.42%) a granular pattern.

The mean age of patients with RP at the last visit was 47.96 ± 17.26 years (range; 3–89). Information about the lens was obtained in 208 patients on their last visit. Cataract developed at a mean age of 42.44 ± 15.84 years (range, 2–86), and 65 (30.09%) were pseudophakic. The mean age at which cataract surgery was performed in the overall sample was 48.30 ± 12.01 years (range, 14–82). No significant differences were found between syndromic and non-syndromic RP or between different inheritance patterns.

The macular status was recorded in 211 patients with RP at their last visit and was preserved in 74 (35.07%), atrophic in 101 (47.87%), and edematous in 36 (17.06%). The BCVA could be analyzed in 195 patients and its distribution throughout life is presented in Fig. 1. Visual field data were available in 190 patients with RP (Fig. 2).

Fifty-eight of 216 (26.85%) RP patients had undergone genetic testing, and 41 (70.68%) out of them were positive (Table 1), although 11 of the remaining 17 patients who were negative had been tested before 2013 before implementation of the NGS techniques. Interestingly, in the group without a genetic diagnosis, 70.6% of subjects had useful remaining vision.

Table 1
Results of genetic tests.

Mode of inheritance	Patients (n)	Disease-causing gene (n)
Autosomal recessive	30	<i>USH2A</i> (17), <i>PDE6A</i> (2), <i>PDE6B</i> (1), <i>CDH23</i> (3), <i>CERKL</i> (1), <i>CLN3</i> (1), <i>CNGA1</i> (1), <i>BBS1</i> (2), <i>CEP290</i> (1) <i>SPATA7</i>
Autosomal dominant	9	<i>RHO</i> (4), <i>PRPF8</i> (2), <i>PRPH2</i> (3)
X-linked	2	<i>RPGR</i> (2)
Other inherited retinal dystrophies		
Autosomal recessive	30	<i>ABCA4</i> (20), <i>CRB1</i> (2), <i>CDHR1</i> (1), <i>BSS1</i> (1), <i>BRAF</i> (1), <i>CABP4</i> (1), <i>TYR</i> (1), <i>OCA2</i> (1), <i>CNGB</i> (1), <i>RPE65</i> (1)
Autosomal dominant	11	<i>PRPH2</i> (5), <i>BEST1</i> (3), <i>OPA1</i> (2), <i>PROM1</i> (1)
X-linked	9	<i>RS1</i> (4), <i>REP1</i> (2), <i>GPR143</i> (2), <i>CACNAF1</i> (1)
Mitochondrial	1	<i>MT-ND1</i> (1)
n: number.		

Concerning IRD other than RP the frequency distribution of each disease, distribution by sex, mean age at symptom onset, and mean age at diagnosis are presented in Table 2. The delay in diagnosis for progressive cone dystrophy and cone-rod dystrophy was 10 years; in central areolar choroidal dystrophy (CACD) 14 years; in Sorsby's fundus dystrophy 7 years; in Best's vitelliform macular dystrophy 8 years; in congenital stationary night blindness 11 years; in congenital achromatopsia 6 years, and in dominant optic atrophy 15 years. The inheritance patterns are presented in Table 3.

Table 2

Inherited retinal diseases other than retinitis pigmentosa: distribution by sex and age at baseline and diagnosis.

Disease	Total N (%)	Women N (%)	Men N (%)	Age at onset Mean $\pm$ SD	Age at diagnosis Mean $\pm$ SD
Panretinal pigmentary retinopathies	39 (14.33%)				
PCD & CORD	25 (9.19%)	14 (56%)	11 (44%)	27 $\pm$ 18.3	37.1 $\pm$ 19.1
LCA	5 (1.84%)	2 (40%)	3 (60%)	2 $\pm$ 1	4 $\pm$ 3.5
BCD	3 (1.1%)	1 (33.3%)	2 (66.7%)	45.7 $\pm$ 12.1	48 $\pm$ 9.5
Retinitis punctata albecens	3 (1.1%)	1 (33.3%)	2 (66.7%)	37 $\pm$ 27.6	38.3 $\pm$ 29.7
CHM	3 (1.1%)	1 (33.3%)	2 (66.7%)	58 $\pm$ 22.3	65.7 $\pm$ 11.7
Macular dystrophies	161 (59.19%)				
STGD, FF	40 (14.7%)	21 (52.5%)	19 (47.5%)	24.1 $\pm$ 13.9	28.1 $\pm$ 15.3
AOFMD	36 (13.2%)	18 (50%)	18 (50%)	60.1 $\pm$ 12.4	62.3 $\pm$ 11.5
CACD	20 (7.35%)	14 (70%)	6 (30%)	42 $\pm$ 14.1	56.2 $\pm$ 16.5
Butterfly-shaped PD	19 (6.99%)	11 (57.9%)	8 (42.1%)	55.3 $\pm$ 14.8	58.2 $\pm$ 14.8
DD	17 (6.65%)	12 (70.6%)	5 (29.4%)	49.3 $\pm$ 5	50.6 $\pm$ 5.2
SFD	14 (.15%)	13 (92.9%)	1 (7.14%)	48.1 $\pm$ 7.5	55.7 $\pm$ 12.5
BVMD	11 (4.04%)	4 (36.4%)	7 (63.6%)	30.5 $\pm$ 17.8	38.5 $\pm$ 20.4

N: number; %: percentage; SD: standard deviation; PCD: progressive cone dystrophy; CORD: cone-rod dystrophy; LCA: Leber's congenital amaurosis; BCD: Bietti's crystalline corneoretinal dystrophy; CHM: choroideremia; STGD: Stargardt's disease; FF: fundus flavimaculatus; AOFMD: adult-onset foveomacular vitelliform dystrophy; CACD: central areolar choroidal dystrophy; PD: pattern dystrophy; DD: dominant drusen; SFD: Sorsby's fundus dystrophy; BVMD: Best's vitelliform macular dystrophy; BCAMD: benign concentric annular macular dystrophy; CSNB: congenital stationary night blindness; ACHM: congenital achromatopsia; DOA: dominant optic nerve atrophy; XLRS: X-linked retinoschisis; FEVR: familial exudative vitreoretinopathy; IRD: inherited retinal disease; n: number.

Disease	Total N (%)	Women N (%)	Men N (%)	Age at onset Mean $\pm$ SD	Age at diagnosis Mean $\pm$ SD
BCAMD	4 (1.47%)	1 (33.3%)	3 (75%)	57 $\pm$ 16	58.3 $\pm$ 15.8
Stationary diseases	28 (10.29%)				
CSNB	14 (5.15%)	2 (14.3%)	12 (85.7%)	7.5 $\pm$ 12.1	18.9 $\pm$ 18.1
Ocular albinism + oculocutaneous albinism	8 (2.94%)	3 (37.5%)	5 (62.5%)	6.3 $\pm$ 8.1	9 $\pm$ 8.4
ACHM + dyschromatopsia	6 (2.21%)	3 (50%)	3 (50%)	10.7 $\pm$ 15.3	16.3 $\pm$ 18.9
Inherited diseases of the optic nerve	12 (4.41%)				
DOA	12 (4.41%)	4 (33.3%)	8 (66.7%)	17.2 $\pm$ 15.1	32.3 $\pm$ 19.7
Hereditary vitreoretinopathies	14 (5.15%)				
XLRS	9 (3.31%)	0	9 (100%)	13.8 $\pm$ 12.6	20.6 $\pm$ 18.6
FEVR	5 (1.84%)	2 (40%)	3 (60%)	44 $\pm$ 23.2	49.6 $\pm$ 19.7

N: number; %: percentage; SD: standard deviation; PCD: progressive cone dystrophy; CORD: cone-rod dystrophy; LCA: Leber's congenital amaurosis; BCD: Bietti's crystalline corneoretinal dystrophy; CHM: choroideremia; STGD: Stargardt's disease; FF: fundus flavimaculatus; AOFMD: adult-onset foveomacular vitelliform dystrophy; CACD: central areolar choroidal dystrophy; PD: pattern dystrophy; DD: dominant drusen; SFD: Sorsby's fundus dystrophy; BVMD: Best's vitelliform macular dystrophy; BCAMD: benign concentric annular macular dystrophy; CSNB: congenital stationary night blindness; ACHM: congenital achromatopsia; DOA: dominant optic nerve atrophy; XLRS: X-linked retinoschisis; FEVR: familial exudative vitreoretinopathy; IRD: inherited retinal disease; n: number.

Disease	Total N (%)	Women N (%)	Men N (%)	Age at onset Mean ± SD	Age at diagnosis Mean ± SD
Other IRD	18 (6.62%)	10 (56.6%)	8 (44.4%)	30.9 ± 18.8	37.2 ± 20.4
Total	272	137 (50.4)	135 (49.6)		
N: number; %: percentage; SD: standard deviation; PCD: progressive cone dystrophy; CORD: cone-rod dystrophy; LCA: Leber's congenital amaurosis; BCD: Bietti's crystalline corneoretinal dystrophy; CHM: choroideremia; STGD: Stargardt's disease; FF: fundus flavimaculatus; AOFMD: adult-onset foveomacular vitelliform dystrophy; CACD: central areolar choroidal dystrophy; PD: pattern dystrophy; DD: dominant drusen; SFD: Sorsby's fundus dystrophy; BVMD: Best's vitelliform macular dystrophy; BCAMD: benign concentric annular macular dystrophy; CSNB: congenital stationary night blindness; ACHM: congenital achromatopsia; DOA: dominant optic nerve atrophy; XLRS: X-linked retinoschisis; FEVR: familial exudative vitreoretinopathy; IRD: inherited retinal disease; n: number.					

Table 3
Pattern of inheritance of each disease.

Disease	Total n	AD n (%)	AR n (%)	XL n (%)	Unknown n (%)
Panretinal pigmentary retinopathies					
PCD and CORD	25	2 (8)	12 (48)	0	11 (44)
LCA	5	0	5 (100)	0	0
BCD	3	0	0	0	3 (100)
Retinitis punctata albescens	3	0	0	0	3 (100)
CHM	3	0	0	3 (100)	0
Macular dystrophies					
STGD, FF	40	0	40 (100)	0	0
AOFMD	36	36 (100)	0	0	0
CACD	20	20 (100)	0	0	0
Butterfly-shaped PD	19	19 (100)	0	0	0
DD	17	17 (100)	0	0	0
SFD	14	14 (100)	0	0	0
BVMD	11	11 (100)	0	0	0
BCAMD	4	4 (100)	0	0	0
Stationary diseases					
CSNB	14	0	0	9 (64)	5 (35.7)
Ocular albinism + oculocutaneous albinism	8	0	2 (25)	2 (25)	4 (50)
ACHM + dyschromatopsia	6	0	3 (50)	3 (50)	0
Inherited diseases of the optic nerve					

PCD: progressive cone dystrophy; CORD: cone-rod dystrophy; LCA: Leber's congenital amaurosis; BCD: Bietti's crystalline corneoretinal dystrophy; CHM: choroideremia; STGD: Stargardt's disease; FF: fundus flavimaculatus; AOFMD: adult-onset foveomacular vitelliform dystrophy; CACD: central areolar choroidal dystrophy; PD: pattern dystrophy; DD: dominant drusen; SFD: Sorsby's pseudoinflammatory fundus dystrophy; BVMD: Best's vitelliform macular dystrophy; BCAMD: benign concentric annular macular dystrophy; CSNB: congenital stationary night blindness; ACHM: congenital achromatopsia; DOA: dominant optic nerve atrophy; XLRS: X-linked retinoschisis; FEVR: familial exudative vitreoretinopathy; AD: autosomal dominant; AR: autosomal recessive; LX: recessive X-linked; n: number.

Disease	Total n	AD n (%)	AR n (%)	XL n (%)	Unknown n (%)
DOA	12	12 (100)	0	0	0
Hereditary viteoretinopathies					
XLRS	9	0	0	9 (100)	0
FEVR	5	5 (100)	0	0	0
Other IRD	18	2 (11.11)	0	0	16 (88.9)
Total	272	142 (52.21)	62 (23)	26 (9.6)	42 (15.4)
PCD: progressive cone dystrophy; CORD: cone-rod dystrophy; LCA: Leber's congenital amaurosis; BCD: Bietti's crystalline corneoretinal dystrophy; CHM: choroideremia; STGD: Stargardt's disease; FF: fundus flavimaculatus; AOFMD: adult-onset foveomacular vitelliform dystrophy; CACD: central areolar choroidal dystrophy; PD: pattern dystrophy; DD: dominant drusen; SFD: Sorsby's pseudoinflammatory fundus dystrophy; BVMD: Best's vitelliform macular dystrophy; BCAMD: benign concentric annular macular dystrophy; CSNB: congenital stationary night blindness; ACHM: congenital achromatopsia; DOA: dominant optic nerve atrophy; XLRS: X-linked retinoschisis; FEVR: familial exudative vitreoretinopathy; AD: autosomal dominant; AR: autosomal recessive; LX: recessive X-linked; n: number.					

Only 71 (26.1%) of the 272 patients diagnosed with an IRD other than RP had a genetic diagnosis, but it was negative in 20 (28.16%). The results are presented in Table 1.

A comparison of our data with results obtained by other research groups is presented in Table 4.

Table 4
Comparison of inherited retinal diseases in the current series with other series.

		Brazil Motta et al. 2018 [15]	Southern France Bocquet et al 2020 [8]	Northern France Puech et al 1991 [16]	Spain Coco et al. 2020
Patients with inherited retinal diseases* (number)		1,246	2,141 (1,608 families)	1,660	488
Positive genetic test/genetic test done		400/559	446/667 families	Not reported	92/129
Positive % of test done		71.57%	66.8% families		71.31%
Positive % of total sample		(32.10%)	(30.11% of families)		(2.95%)
Panretinal pigmentary retinopathies	Non-syndromic retinitis pigmentosa	433/1,246 34.75%	922/2,141 43.06%	584 – 45/1,660 37.89%	182/488 37.29%
	Syndromic retinitis pigmentosa	145/1,246 11.63%	268/2,141 12.52%	105/1,660 6.32%	34/488 6.96%
	Progressive cone dystrophy and cone-rod dystrophy	89/1,246 7.14%	91 – 49/2,141 6.54%	111 – 33/1,660 8.67%	25/488 5.12%
Macular dystrophies	Stargardt and/or fundus flavimaculatus	257/1,246 20.62%	118/2,141 5.51%	286+31/1,660 19.09%	40/488 8.19%
	Best disease	26/1,246 2.08%	43/2,141 2.01%	106/1,660 6.38%	11/488 2.25%
	Other	108/1,246 (105 undetermined) 8.67%	188/2,141 8.78%	73/1,660 4.39%	110/488 22.54%
*Non-syndromic retinitis pigmentosa, progressive cone dystrophy and cone-rod dystrophy not included in this study					

Discussion

The current study presents interesting data about the relative frequencies of inherited retinal diseases and their clinical appearance, inheritance patterns, age at diagnosis, and results of genetic testing in a Spanish region with 2,500,000 inhabitants.

As expected, RP was the most frequently inherited retinal disease found in the current study. The RP frequencies vary little between published studies and range from 34.75–43.06% [8, 15, 16]. Even the group of syndromic RPs as a whole had similar frequencies (Table 4). Usher syndrome was the most frequent form of syndromic pigmentary retinopathy as reported previously [8, 15, 16]. Regarding macular dystrophies, Stargardt's disease was the most frequently seen entity in the current study and in most studies but with important variations ranging from 5.51% reported by Bocquet et al. in Southern France to 20.62% reported by Motta et al. in Brazil [8, 15]. The reported frequencies of other macular dystrophies vary widely among studies of different populations, and the current study has the higher percentage [8, 15, 16]. Such wide variations can be due to several factors: it is unclear if some macular dystrophies included in the current study also were included in other studies; the definite diagnosis of a particular macular dystrophy can be challenged; moreover, geographic variations in the frequency of some mutations can promote geographic disparities in the frequency of some entities as happens with the higher rate of CACD in the Spanish population compared with others [17, 18]. Although consanguinity can play an important role in the prevalence of IRD in some populations [19], the current study had consanguinity data, including relative consanguinity data (11.11% and 17.46%, respectively), similar to those published in most populations [15, 20].

Concerning the inheritance patterns in the RP group, the rate of AR inheritance in the current sample was high (53.61% vs. 16.0%-39% in other studies), while sporadic cases occurred less frequently than in other studies (24.23% vs. 40%-51% in other studies) [4, 21–24]. Nevertheless, 28 patients in our sample did not provide family history data and thus they were not included in this analysis; if they had been considered as sporadic cases, this figure would have approached 50%.

Within the RP group, the ERG was abolished or diminished in most patients, similar to data reported by Berson et al [20, 25].

With small variations, the clinical presentations of IRDs in the current sample was similar to those already described. Regarding the ocular fundus, most had the classic pattern of pigmentation in the spicules. The percentage of cataract patients (39.42%) was similar to the data provided by Testa et al [24]. and slightly lower than in other studies (45%-52%) [26]; the group of pseudophakic patients among the current cases (31.25%) was greater than that found in the other studies (15.4%-20%). [10, 27–29] The mean age at the time of cataract surgery was similar to those reported previously [27–29]. Finally, the prevalence of macular edema in our RP sample (17.06%) was lower than in other studies (23%-50%) [10, 30–31], although it was similar to that reported by Hirakawa et al [32]. Genetic diagnosis of IRDs is desirable for many reasons because it can provide a definitive diagnosis, which can deliver great relief to patients and families; it also helps physicians to better define the inheritance pattern and the risk for the remaining

family members, and it is crucial to identify patients for potential enrollment in clinical trials or new advanced therapies. Besides, 71.6% of the patients in the current series without a genetic study had good remaining vision, so they could be candidates for gene therapy. The first important difficulty for genetic diagnosis of IRDs is that the clinical diagnosis of different phenotypes may be due to the same mutation and vice versa [33]. Thus, the wide variety of IRDs and their relative low frequency make it difficult for the general ophthalmologist and the retinal specialist to establish an accurate diagnosis and focus the search on one or a small number of gene mutations. Another important factor is the possibility for ophthalmologists and patients to access a clinical genetic unit. In our case, Castilla y Leon region lacks a genetic unit. These reasons explain the low rates of genetic diagnoses obtained in the current study (22.95%), which was slightly lower than those published in other such studies (30.11% and 32.10%) [8, 15].

Delayed diagnoses are common problems in IRDs and may result from deferral of patients with referring symptoms and/or the inexperience of doctors who first treated them. Data from the Survey of the Delay in Diagnosis for Rare Diseases in Europe confirm that this delay generally occurs in the diagnosis of any rare disease [34]. Moreover, late diagnosis of stable diseases may be due in part to their moderate visual impairment and minimal fundus changes in children who do not complain [35]. Entities with a more characteristic phenotype can be recognized early, but in many cases a conclusive diagnosis of an IRD cannot be made until several visits and electrophysiologic and imaging evaluations are performed and interpreted correctly.

The major strength of the current study was that the patients were part of ordinary specialized practices and the sample size was adequate considering that the diseases are rare. It also emphasizes the need to improve access to genetic testing in our population.

But the current study has important limitations. First, the sample size of each disease was small except for that of RP. However, these are rare diseases and, in this context, relevant findings could be highlighted. Another constraint was the heterogeneity in the follow-up of the patients (some, up to 20 years of follow-up and others, only infrequent visits). In addition, the presence of macular edema may have been underestimated, especially in patients with few visits during the first years in which optical coherence tomography was unavailable, although this happened only in a small number of patients. A major problem was that the vast majority of patients do not have a molecular diagnosis and the state-of-the-art in IRD is based on both clinical and molecular diagnosis. In this context comments about inheritance patterns must be taken with caution. Finally, many of the genetic studies with negative results were very old and patients need to be reassured using NGS techniques. Nevertheless, this is something we wanted to point out to be able to ask regional management for a change in their policy denying test to this group of patients and families.

Knowing the rate of genetic testing in actual clinical practice can be a good starting point to plan future actions such as genetic studies with new diagnostic techniques for as many subjects as possible, which

would allow classification of the pathology from the genotypic point of view in our population, to move forward in the search for new mutations and properly diagnose patients with doubtful diagnoses.

Conclusions

Only 27.31% of the patients with RP and 26.1% of the rest of the IRDs had undergone genetic testing, but in more than two thirds (71.31%) of those with RP the test results were positive and facilitated the identification of more causative mutations and genes in our population. Most RP patients (71.6%) had residual vision, which allows them to be candidates for treatments aimed at preserving their vision, and we need to promote their prompt genetic diagnosis. The current study confirmed the substantial delays in diagnosing most of these diseases and the need to perform more genetic studies in our region what also worries us. By highlighting our weaknesses we want to move regional managers to improve these data.

Declarations

Ethics approval and consent to participate

This Study was declared in accordance with ethical standards Hospital Universitario Rio Hortega and the Clinical Research Ethics Committee -Health Area East- of Valladolid (CEIC-VA-EAST-HCUV) with the reference number PI 18-1171TFMNOHCUV;. Administrative permissions were acquired by our team to access the data used in our research.

Consent for publication

Not applicable. A written informed consent was obtained from all patients.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors report no conflict of interest.

Financial support

This study received no funding.

Authors' contributions

RMC concived and coordinated the study. RMC, MDA, AOM, MRS and HST participated on the design of the study. RMC and HST were the Ophthalmologist who attended the patients. RMC, MDA and AOM reviewed the patient's charts to collect data. RMC, MDA, AOM and HST analyzed the data. RMC, MRS and

MDA wrote the final manuscript. RMC, MRS and HST revised critically the work. All authors read and approved the final manuscript.

Acknowledgements

None.

References

1. Traboulsi EI. Hope and major strides for genetic diseases of the eye. *J Genet*. 2009;88(4):395–7.
2. Chizzolini M, Galan A, Milan E, et al. Good epidemiologic practice in retinitis pigmentosa: from phenotyping to biobanking. *Curr Genomics*. 2011;12(4):260-6.
3. KH Na, HJ Kim, KH Kim, et al. Prevalence, age at diagnosis, mortality, and cause of death in retinitis pigmentosa in Korea-a nationwide population-based study. *Am J Ophthalmol*. 2017;176(4):157-65.
4. Bertelsen M, Jensen H, Bregnhøj JF, Rosenberg T. Prevalence of generalized retinal dystrophy in Denmark. *Ophthalmic Epidemiol*. 2014;21(4):217-223.
5. Bakkar MM, Alzghoul EA, Haddad MF. Clinical characteristics and causes of visual impairment in a low vision clinic in northern Jordan. *Clin Ophthalmol*. 2018;12:631-7.
6. Muñoz-Cuellar JC, RM. Clinical Characterization and Frequency of Observation of Hereditary Retinal Diseases: Multicentric Study in Panama in 2012-2013. *Journal of Pharmacy and Pharmacology*. 2016(4):618-30.
7. Bocquet B, Lacroux A, Surget MO, Baudoin C, Marquette V, Manes G, et al. Relative frequencies of inherited retinal dystrophies and optic neuropathies in Southern France: assessment of 21-year data management. *Ophthalmic Epidemiol*. 2013;20(1):13-25.
8. Hamel C. Retinitis pigmentosa. *Orphanet J Rare Dis*. 2006;1:40.
9. Verbakel SK, van Huet RAC, Boon CJF, den Hollander AI, Collin RWJ, Klaver CCW, et al. Non-syndromic retinitis pigmentosa. *Prog Retin Eye Res*. 2018;66:157-86.
10. Costa KA, Salles MV, Whitebirch C, Chiang J, Sallum JMF. Gene panel sequencing in Brazilian patients with retinitis pigmentosa. *Int J Retina Vitreous*. 2017;3:33.
11. Gill JS, Georgiou M, Kalitzeos A, Moore AT, Michaelides M. Progressive cone and cone-rod dystrophies: clinical features, molecular genetics and prospects for therapy. *Br J Ophthalmol*. 2019.
12. Clinical Trials Database. U.S National Library, Bethesda. 2000. <https://clinicaltrials.gov>. Accessed 28 apr 20.
13. Holladay JT. Visual acuity measurements. *J Cataract Refract Surg*. 2004;30(2):287-90.
14. Motta FL, Martin RP, Filippelli-Silva R, Salles MV, Sallum JMF. Relative frequency of inherited retinal dystrophies in Brazil. *Sci Rep*. 2018;8(1):15939.
15. Puech B, Kostrubiec B, Hache JC, Francois P. [Epidemiology and prevalence of hereditary retinal dystrophies in the Northern France]. *J Fr Ophtalmol*. 1991;14(3):153-64.

16. Gamundi MJ, Hernan I, Muntanyola M, Trujillo MJ, Garcia-Sandoval B, Ayuso C, et al. High prevalence of mutations in peripherin/RDS in autosomal dominant macular dystrophies in a Spanish population. *Mol Vis*. 2007;13:1031-7.
17. Tishkoff SA, Kidd KK. Implications of biogeography of human populations for 'race' and medicine. *Nat Genet*. 2004;36(11 Suppl):S21-7.
18. Nirmalan PK, Krishnaiah S, Nutheti R, Shamanna BR, Rao GN, Thomas R. Consanguinity and eye diseases with a potential genetic etiology. Data from a prevalence study in Andhra Pradesh, India. *Ophthalmic Epidemiol*. 2006;13(1):7-13.
19. Berson EL, Rosner B, Simonoff E. Risk factors for genetic typing and detection in retinitis pigmentosa. *Am J Ophthalmol*. 1980;89(6):763-75.
20. Ayuso C, Garcia-Sandoval B, Najera C, Valverde D, Carballo M, Antinolo G. Retinitis pigmentosa in Spain. The Spanish Multicentric and Multidisciplinary Group for Research into Retinitis Pigmentosa. *Clin Genet*. 1995;48(3):120-2.
21. Najera C, Millan JM, Beneyto M, Prieto F. Epidemiology of retinitis pigmentosa in the Valencian community (Spain). *Genet Epidemiol*. 1995;12(1):37-46.
22. Boughman JA, Fishman GA. A genetic analysis of retinitis pigmentosa. *Br J Ophthalmol*. 1983;67(7):449-54.
23. Testa F, Rossi S, Colucci R, Gallo B, Di Iorio V, della Corte M, et al. Macular abnormalities in Italian patients with retinitis pigmentosa. *Br J Ophthalmol*. 2014;98(7):946-50.
24. Berson EL. Light deprivation and retinitis pigmentosa. *Vision Res*. 1980;20(12):1179-84.
25. Fujiwara K, Ikeda Y, Murakami Y, Funatsu J, Nakatake S, Tachibana T, et al. Risk Factors for Posterior Subcapsular Cataract in Retinitis Pigmentosa. *Invest Ophthalmol Vis Sci*. 2017;58(5):2534-7.
26. Jackson H, Garway-Heath D, Rosen P, Bird AC, Tuft SJ. Outcome of cataract surgery in patients with retinitis pigmentosa. *Br J Ophthalmol*. 2001;85(8):936-8.
27. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. *Lancet*. 2006;368(9549):1795-809.
28. Liew G, Moore AT, Bradley PD, Webster AR, Michaelides M. Factors associated with visual acuity in patients with cystoid macular oedema and Retinitis Pigmentosa. *Ophthalmic Epidemiol*. 2018;25(3):183-6..
29. Hagiwara A, Yamamoto S, Ogata K, Sugawara T, Hiramatsu A, Shibata M, et al. Macular abnormalities in patients with retinitis pigmentosa: prevalence on OCT examination and outcomes of vitreoretinal surgery. *Acta Ophthalmol*. 2011;89(2):e122-5.
30. Hajali M, Fishman GA, Anderson RJ. The prevalence of cystoid macular oedema in retinitis pigmentosa patients determined by optical coherence tomography. *Br J Ophthalmol*. 2008;92(8):1065-8.
31. Hirakawa H, Iijima H, Gohdo T, Tsukahara S. Optical coherence tomography of cystoid macular edema associated with retinitis pigmentosa. *Am J Ophthalmol*. 1999;128(2):185-91.

32. Battu R, Mallipatna A, Elackatt NJ, Schouten J, Webers CAB. Challenges of managing retinal dystrophies: An experience from south India. *Ophthalmic Genet.* 2018;39(1):1-3.
33. EURORDIS: European Organization for Rare Diseases. Eurordis policy fact sheet. https://www.eurordis.org/sites/default/files/publications/Fact_Sheet_Eurordiscare2.pdf (2013). Accessed 28 nov 19.
34. Zeitz C, Robson AG, Audo I. Congenital stationary night blindness: an analysis and update of genotype-phenotype correlations and pathogenic mechanisms. *Prog Retin Eye Res.* 2015;45:58-110.

Figures

Figure 1

Percentages of patients based on low-vision categories. The figure shows the percentages of patients according to the decade of life for the total retinitis pigmentosa sample. A higher number of patients without Low Vision (LV) or with mild LV is observed in the first decades, which decreases throughout life while blind patients increase.

Figure 2

Percentages of patients based on the status of the visual field according to the decade of life for the total retinitis pigmentosa sample. The figure shows the percentages of patients according to the decade of life for the total retinitis pigmentosa sample. The number of analysed patients is very small in the first and last decades of life, so these percentages should be taken with caution. Unrecordable CVs or lower than 5 degrees preserved increase from the 2nd to the 7th decades of life, and those greater than 5 degrees decrease as expected.